

Hoechst



Hoechst Aktiengesellschaft
Pharma Research
Toxicology
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Primary Skin Irritation of a preparation of
1 % Octopirox, 0.33 % citric acid,
75.0 % PEG 400 and 23.67 % water (pH 7.0)
in rabbits (patch test).
Report No 736/79

Summary:

A patch test for skin tolerance carried out under the experimental conditions laid down in the FDA guide lines showed that this Octopirox preparation was slightly irritant to the skin.

The PEG 400 - water mixture used as a control proved to be non-irritant according to the FDA guide lines.

Materials and Methods

Albino Himalayan rabbits (Stock: Hoe: HIMK (SPFWiga); own breed) of 1.5 to 2.0 kg weight were used as experimental animals. They were kept in cages on their own and received standard feed ERKA 8300 (Feeding stuff manufacturer Robert Koch OHG, Hamm/Westf.). Feed and water were offered in unlimited quantities.

The substance "Octopirox^R" = H 72 6146 A was supplied in a 1 % solution in 0.33 % citric acid, 75,0 % PEG 400 and 23.67 % water. The pH of the colourless solution was adjusted to 7.0. The vehicle PEG 400 - water (3 : 1) was used as a control on the same animals.

The experiment was carried out during the period 06.11. to 09.11.79.

Experimental procedure:

An area of at least 6 x 3 cm on both flanks of six rabbits was shaved with an electric razor. One half of each shaved area was, in addition, abraded with a scarifier.

The substance under test and the vehicle on its own were applied in 0.5 ml quantities on pieces of gauze sized 2.5 x 2.5 cm. They were attached to the prepared skin with strips of adhesive plaster and covered with inert, impervious PVC film, 6 - 8 cm wide, and an elastic bandage was then wound round the animals' trunks. The period of application was 24 hours, at the end of which time the bandages were removed and the first inspection carried out, followed by further assessment at 24 and 72 hours.

The findings were used to determine the primary irritation score according to para 1500.41 of Federal Register 38, No 187, 27.09.1973, p 27019 (Appendix 1).

Results:

The Octopirox preparation produced a primary irritation score of 1.9. After 24 hours of application, the scarified skin of three animals showed a severe degree of erythema formation, and the same applied to the intact skin of two of these three animals. Otherwise, there was only mild, hardly perceptible erythema and oedema. According to the FDA guide lines, the 1 % solution of Octopirox in PEG 400 - water mixture must be considered as slightly irritant.

The polyethylene glycol 400 - water mixture in a proportion of 3 : 1 used as a control induced a mild, hardly noticeable swelling of the scarified and intact site of application in one experimental animal. This means that the PEG 400 - water mixture is non-irritant.

Dr. L/Bo
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Appendix
Classification

Evaluation of Primary Skin Irritation
(Patch Test after FDA)

The table is reproduced from U.S. Code of Federal Regulations § 1500.41 "Method of testing primary irritant substances" as published in Federal Register 38, 27019 (1973).

	<u>Value</u>
1. Erythema and Eschar Formation	
No erythema	0
Very slight erythema (barely perceptible)	1
Well defined erythema	2
Moderate to severe erythema	3
Severe erythema (beet redness) to slight eschar formation (injuries in depth)	4
2. Edema Formation	
No edema	0
Very slight edema (barely perceptible)	1
Slight edema (edges of area well defined by definite raising)	2
Moderate edema (raised approximately 1 mm)	3
Severe edema (raised more than 1 mm and extending beyond area of exposure)	4

"The 'value' recorded for each reading is the average value of the six or more animals subject to the test.

Add the values for erythema and eschar formation at 24 and 72 hours for intact skin to the values on abraded skin at 24 and 72 hours (four values). Similarly, add the values for edema formation at 24 and 72 hours for intact and abraded skin (four values). The total of the eight values is divided by four to give the primary irritation score."

Evaluation

0.0 - 0.5	Non-irritant	(nicht reizend)
0.6 - 3.0	Slightly irritant	(leicht reizend)
3.1 - 5.0	Moderately irritant	(mäßig reizend)
5.1 - 8.0	Severely irritant	(stark reizend)

DERMAL TOLERANCE - PATCH TEST																Study No.:					
Substance: Octopirox R (in PEG 400/water)										Dose: 2 x 0,5 ml/g on 3 x 3 cm skin surface						Investigator: Böcher / Vatter					
Concentration: Original				Application intact h flank scarif. f flank r						Species: Albino Himalayan rabbit						Study start: 06.11.1979					
Time after apol.				24 h						48 h						72 h					
Animal No.				151	152	153	154	155	156	151	152	153	154	155	156	151	152	153	154	155	156
scarified		Erythema	1	1	1	3	3	3	1	1	1	2	2	3	0	0	0	1	1	1	
		Edema	1	1	2	1	1	2	1	1	1	0	0	1	0	1	1	0	0	1	
intact		Erythema	1	1	1	3	1	3	1	0	1	2	1	2	0	0	0	1	0	0	
		Edema	1	2	1	1	1	2	1	1	1	0	0	0	0	0	1	0	0	0	
Sum			38						24						8						
Skin dry, rough																					
Skin with fine scales																					
Skin with coarse scales																					
Skin hardened																					
Skin raised																					
Skin parchment-like																					
Skin chapped (superf.)																					
Skin chapped (deep)																					
Eschar formation																					
Necrosis																					
Desquamation, small-sized																					
Desquamation, large-sized																					
Open wound																					
Exudation (clear)																					
Exudation (reddish)																					
Scratch marks																					
Discolorations			isolated																		
			extensive																		
primary irritation index: Sum of all rabbits, 24 + 72 h-value= 46: 24= 1,9																					
Remarks: h = hindflank r = right f = foreflank																					

Annex
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DERMAL TOLERANCE - PATCH TEST																	Study No.:					
Substance: PEG 400 / water										Dose: 2 x 0,5 ml/g on 3 x 3 cm skin surface							Investigator: Böcher / Vatter					
Concentration: Original				Application intact h flank 1 scarif. f flank				Species: Albino Himalayan rabbit				Study start: 06.11.1979										
Time after appl.				24 h				48 h				72 h										
Animal No.				151	152	153	154	155	156	151	152	153	154	155	156	151	152	153	154	155	156	
scarified				Erythema	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
				Edema	0	0	1	0	0	0	0	0	0	1	0	0	0	0	0	0	1	0
intact				Erythema	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
				Edema	0	0	1	0	0	0	0	0	0	1	0	0	0	0	0	0	1	0
Sum				2				2				2										
Skin dry, rough																						
Skin with fine scales																						
Skin with coarse scales																						
Skin hardened																						
Skin raised																						
Skin parchment-like																						
Skin chapped (superf.)																						
Skin chapped (deep)																						
Eschar formation																						
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Open wound																						
Exudation (clear)																						
Exudation (reddish)																						
Scratch marks																						
Discolorations																						
isolated																						
extensive																						
primary irritation index: Sum of all rabbits, 24 + 72 h-value= 4 : 24= 0,2																						
Remarks: h = hindflank 1 = left f = foreflank																						